World Journal of Clinical Case Reports and Case Series

Case Series

Add-on Treatment with Blonanserin for Clozapine-Resistant Schizophrenia: Three Case Reports

Yu Fang, Ping Guo, Liang LV, Min Feng, Shanfei Cheng, Mincai Qian, Shikai Wang and Huanxin Chen*

Department of Psychiatry, Huzhou Third Municipal Hospital, The Affiliated Hospital of Huzhou University, China

Abstract

Clozapine is the treatment choice for Treatment-Resistant Schizophrenia (TRS), but 40% to 70% patients with TRS remain inadequately treated despite clozapine treatment, known as Clozapine-Resistant Schizophrenia (CRS). CRS's current treatment combines clozapine with other antipsychotics or physical therapy, but the outcome is still unsatisfactory. Blonanserin is a new atypical antipsychotic which processes advantages over other antipsychotics. We concurrent treated three cases of CRS with blonanserin successfully, with the dosage and side effects of clozapine reduced. Therefore, concurrent treatment with blonanserin is highly relevant for improving the prognosis of patients with TRS or CRS.

Keywords: Treatment-resistant schizophrenia; Clozapine-resistant schizophrenia; Add-on treatment; Blonanserin; Clozapine

Introduction

Treatment-Resistant Schizophrenia (TRS) comprises about 30% to 40% of patients with schizophrenia, referring to those with poor improvement to adequate medications [1]. Clozapine is the treatment choice for TRS patients, but 40% to 70% remain inadequately treated despite clozapine treatment, known as Clozapine-Resistant Schizophrenia (CRS) [2]. CRS's current treatment combines clozapine with other antipsychotics or physical therapy, but the outcome is still unsatisfactory [3].

Blonanserin is a new atypical antipsychotic which processes advantages over other antipsychotics [4], and was shown to be effective for TRS and CRS [5-7]. We present three cases of CRS diagnosed with the criteria reported in the previous study [2] that concurrent treated with blonanserin successfully.

Case Presentation

Case 1

Mr. L is a 33-year-old man with a four-year history of schizophrenia. His symptoms included auditory hallucinations and associated persecutory delusions. Mr. L got no improvement in his symptoms after previous treatment with clozapine (up to 225 mg/d), olanzapine, amisulpride and risperidone and 12 sessions of Modified Electroconvulsive Therapy (MECT). At admission, Mr. L was being treated with clozapine 100 mg/d and amisulpride 0.4 g/d. He was experiencing sialorrhea and had involuntary labial tremors. After concurrent treatment with blonanserin, Mr. L's auditory hallucinations and delusions improved significantly within a week (Table 1). His involuntary labial tremor disappeared after amisulpride was discontinued. The patient's auditory hallucination remitted and his social function improved during a 2 years follow-up with clozapine 50 mg/d and blonanserin 4 mg tid.

Case 2

Ms. Z is a 31-year-old female with a 12-year history of schizophrenia. Despite prior treatment with olanzapine, clozapine (up to 250 mg/d), ziprasidone and aripiprazole, she continued to experience auditory hallucinations, talking and laughing to herself and could not work. Despite treatment with clozapine 175 mg/d (Serum Concentration 200.0 ng/mL), aripiprazole 10 mg/d, and paliperidone 6 mg/d, she continued to experience social withdrawal and auditory hallucinations. She also took metoprolol 47.5 mg/d for tachycardia, lactulose oral liquid 15 ml/d for constipation and benzhexol 4 mg/d for sialorrhea. After admission, aripiprazole and paliperidone were discontinued, and blonanserin was initiated from 4mg bid and increased to 4 mg tid. Clozapine doses were gradually reduced to 25 mg/d, and benzhexo, metoprolol and lactulose oral liquid was discontinued. After 2 weeks, Ms. Z's auditory hallucinations and her self-talk and self-laughing behaviors were eliminated (Table 1). During a six-month follow-up, the patient's improvement remained stable on this treatment regimen and she was able to do simple work.

Case 3

Ms. D is a 33-year-old divorced female with a 15-year history of schizophrenia who has been hospitalized many times. Prior to hospitalization she had been treated with clozapine (up to 300 mg/d), aripiprazole, and risperidone at adequate doses and for adequate durations. At her admission, Ms. D was being treated with clozapine 250 mg/d (Fasting Serum Concentration 552.0 ng/mL) and aripiprazole 10 mg/d, but she continued to experience persistent auditory hallucinations, delusions of persecution, self-talking and self-laughing behaviors, social withdrawal and poor insight into her illness. After admission, her clozapine dose was reduced to 200 mg/d and blonanserin was initiated and titrated to 8 mg/d. After 3 days, her serum concentration of clozapine was 757.0 ng/ml. The dose of blonanserin was increased to 10 mg bid, and the dosage of clozapine was reduced to 100 mg/d at week 4 mg/d and 50 mg/d at week 8.

Citation: Fang Y, Guo P, Liang LV, Feng M, Cheng S, Qian M, et al. Add-on Treatment with Blonanserin for Clozapine-Resistant Schizophrenia: Three Case Reports. World J Clin Case Rep Case Ser. 2023;3(2):1019.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Nov 15th, 2023

***Corresponding author:** Shikai Wang, Department of Psychiatry, Huzhou Third Municipal Hospital, The Affiliated Hospital of Huzhou University, Huzhou City, Zhejiang, 313000, China, Tel: +86-13665752769

Table 1: Changes of Scores (and reduction %) of PANSS and its sub-scales in the timeline of the three cases.

	Scale and sub-scale	V0- Baseline	V1- D1	V2- Day 3	V3- Week 1	V4- Week 2	V5- Week 4	V6- Week 8	V7- Week 12
Case 1	PANSS	101	99 (2.8)	90 (15.5)	82 (26.8)	75 (36.6)	68 (46.5)	64 (52.1)	59 (59.2)
	Positive	26	26 (0)	20 (31.6)	15 (57.9)	14 (63.2)	11 (78.9)	10 (84.2)	10 (84.2)
	Negative	24	24 (0)	23 (5.9)	21 (17.6)	19 (29.4)	19 (29.4)	18 (35.3)	17 (41.2)
	General Psycho-pathology	51	49 (5.7)	47 (11.4)	46 (14.3)	42 (25.7)	38 (37.1)	36 (42.9)	32 (54.3)
Case 2	PANSS	89	90 (-1.7)	86 (5.1)	82 (11.9)	72 (28.8)	67 (37.3)	60 (49.2)	57 (54.2)
	Positive	17	17 (0)	13 (40)	13 (40)	10 (70)	9 (80)	8 (90)	8 (90)
	Negative	27	27 (0)	26 (5)	26 (5)	24 (15)	22 (25)	18 (45)	17 (50)
	General Psycho-pathology	45	46 (-3.4)	45 (0)	43 (6.9)	38 (24.1)	36 (31.0)	34 (37.9)	32 (44.8)
Case 3	PANSS	96	98 (-3.0)	94 (3.0)	90 (9.1)	84 (18.2)	72 (36.4)	66 (45.5)	65 (47.0)
	Positive	24	24 (0)	22 (11.8)	19 (29.4)	16 (47.1)	11 (76.5)	9 (88.2)	9 (88.2)
	Negative	24	24 (0)	23 (5.9)	23 (5.9)	22 (11.8)	20 (23.5)	19 (29.4)	18 (35.3)
	General Psycho-pathology	48	50 (-6.3)	49 (-3.1)	48 (0)	46 (6.3)	41 (21.9)	38 (31.3)	38 (31.3)

Note: Reduction of total score of PANSS=(V0-Vn)/(V0-30); Reduction of score of positive sub-scale=(V0-Vn)/(V0-7); Reduction of score of negative sub-scale=(V0-Vn)/(V0-7); Reduction of score of general Psychopathology sub-scale=(V0-Vn)/(V0-16).

Ms. D's auditory hallucinations and self-talk behaviors gradually disappeared (Table 1). She was discharged after 6 weeks, and her psychiatric symptoms remained well controlled during two years follow-up.

Discussion

Previous studies indicated that about 50% to 70% of TRS cases are induced by Dopamine Ultra-sensitivity Psychosis (DSP), which may be related to excessive blocking of dopamine D_2 receptor (DRD_2) and the up-regulation of DRD_2. Blonanserin is a highly selective D_2 and D_3, and 5-HT2 receptor antagonist (DSA)[4], and it can quickly penitrate the blood brain barriar, combine with DRD_2 easily and stably, reducing the fluctuation of DRD_2 occupancy ratio in the brain, and reduce the ultra-sensitivity of dopamine in TRS patients. Previous studies have found that blonanserin had a rapid effect for patients with schizophrenia, including social function [8]. It was also reported that blonanserin is effective for TRS and CRS [6,7].

In this report, all three patients suffered by CRS. However, the patient's symptoms and social function rapidly improved after adding blonanserin. The dosage of clozapine reduced, and its adverse reactions were eliminated. Other mechanisms of blonanserin to improve CRS patients may lie in: firstly, the terminal half-life of blonanserin could extend up to about 70 hours after multiple doses, further reducing the fluctuation of DRD_2 occupancy level. Secondly, higher D_2/5-HT_{2A} may lead to better clinical efficacy. Thirdly, blonanserin has multiple antagonistic effects for dopamine D_2 receptor, D_3 receptor, 5-HT_{2A} receptor, and partial 5-HT_{1A} receptor, which may contribute to the treatment of TRS or CRS. It should be pointed out that after adding blonanserin in Case 3, the serum concentration of clozapine kept increasing significantly even after the dosage of clozapine was reduced, indicating that blonanserin may affect clozapine metabolism by cytochrome P450 3A4, a metabolic pathway of clozapine.

As the only drug approved by the FDA for TRS treatment, clozapine has certain advantages in treating schizophrenia [2]. However, the potential hazards of clozapine cannot be ignored, including granulocytopenia, cardiotoxicity, metabolic syndrome, intestinal obstruction, aspiration pneumonia, and secondary obsessive-compulsive disorder. Therefore, developing new approaches [9], such as concurrent treatment with blonanserin, is highly relevant for improving the prognosis of patients with TRS or CRS.

Conclusion

Clozapine is the treatment choice for TRS, but the potential hazards of clozapine cannot be ignored. Blonanserin is a new atypical antipsychotic which processes advantages, and concurrent treatment with blonanserin might be a potential strategy for improving the prognosis of patients with TRS or CRS.

Funding

This work was supported by the Project of Huzhou Municipal Science and Tech Commission (No. 2020GYB46).

References

1. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. American Psychiatric Association; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(2 Suppl):1-56.
2. Wagner E, Kane JM, Correll CU, Howes O, Siskind D, Honer WG, et al. Clozapine Combination and Augmentation Strategies in Patients with Schizophrenia-Recommendations from an International Expert Survey Among the Treatment Response and Resistance in Psychosis (TRRIP) Working Group. Schizophr Bull. 2020;46(6):1459-70.
3. Chakrabarti S. Clozapine resistant schizophrenia: Newer avenues of management. World J Psychiatry. 2021;11(8):429-48.
4. Ohno Y, Okano M, Imaki J, Tatara A, Okumura T, Shimizu S. Atypical antipsychotic properties of blonanserin, a novel dopamine D2 and 5-HT2A antagonist. Pharmacol Biochem Behav. 2010;96(2):175-80.
5. Kurotaki N, Nobata H, Nonaka S, Nishihara K, Ozawa H. Three cases of schizophrenia showing improvement after switching to blonanserin. Psychiatry Clin Neurosci. 2011;65(4):396-7.
6. Takaki M, Okahisa Y, Kodama M, Mizuki Y, Sakamoto S, Ujike H, et al. Efficacy and tolerability of blonanserin in 48 patients with intractable schizophrenia. Acta Neuropsychiatr. 2014;24(6):380-3.
7. Takaki M, Takahashi S, Yada Y, Kitagawa K, Kishi Y, Yamada N. Case Report: Augmentation with Blonanserin for a Schizophrenia Patient with Insufficient Response to Clozapine. Open J Psychiatry. 2018; 8(2):131-6.
8. Hori H, Yamada K, Kamada D, Shibata Y, Katsuki A, Yoshimura R, et al. Effect of blonanserin on cognitive and social function in acute phase Japanese schizophrenia compared with risperidone. Neuropsychiatr Dis Treat. 2014;10:527-33.
9. Farooq S, Choudry A, Cohen D, Naeem F, Ayub M. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. BJPsych Bull. 2019:43(1):8-16.